REMARKS

Upon entry of the claim amendments, Claims 1 and 18-23 will be all the claims pending in the application.

Applicants have made non-narrowing, editorial amendments to Claims 1, 18-12 and 23. Claim 24 has been canceled. No new matter has been added.

I. Section No. 3: Rejection Under 35 U.S.C. § 103

Claims 1 and 18-24 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Sato, *et al* (Journal of Medicinal Chemistry).

Applicants respectfully traverse.

The present specification contains objective evidence of patentability, and in particular, objective evidence of the unexpected superiority of the claimed compound, which serves to rebut any alleged *prima facie* case of obviousness.

At page 3 of the Action, the Examiner states (emphasis added):

> H v. Me is not deemed patentably distinct ***absent evidence of superior or unexpected properties***.

At page 3, the Examiner also states:

> Furthermore, applicants should note a replacement of two methyl groups on a known compound with two hydrogen atoms has been held to be prima facie obvious due to close structural similarity.

In response, Applicants point out that evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, rebuts a *prima facie* case of obviousness. In re Chupp, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). In fact, evidence that a compound is unexpectedly superior in just one of a spectrum of common properties rebuts a *prima facie* case of obviousness. Id.

In order to prove that the claimed compound is unexpectedly superior over the prior art, Applicants would like to direct the Examiner's attention to Test Examples 2 and 4, at pages 37-38 and 39-40, respectively, and in particular, to the tables at pages 38 and 40 of the specification.

Test Example 2 includes a comparison between Example 1(b) of the present specification and hydrochloride of 5-chloro-7-methyl-2-(4-methyl-1-homopiperazinyl)benzoxazole (E). Example 1(b), which is set forth at page 25 of the specification, describes the preparation of a compound according to the presently claimed invention. As for hydrochloride of 5-chloro-7-methyl-2-(4-methyl-1-homopiperazinyl)benzoxazole (E), it is the same compound as Sato's compound 6v.

Thus, Test Example 2 is an objective comparison between the claimed subject matter and the closest prior art. In re Burckel, 201 USPQ 67 (CCPA 1979). In particular, Test Example 2 at pages 37-38 is an objective comparison between the claimed subject matter and Sato's compound 6v in the context of inhibition action for rat diarrhea under restriction stress. Such a comparison is to be given maximum weight in determining the issue of nonobviousness.

The comparison in Test Example 2 demonstrates that the claimed compound exhibits inhibition action for rat diarrhea under restriction stress that is superior to that for Sato's compound 6v. That is, the presently claimed compound has unexpectedly superior suppressing action against diarrhea than Sato's compound 6v, and in particular, ten times or more potent suppressing action against diarrhea in the experiments conducted *in vivo* than Sato's compound 6v, which the Examiner considers structurally similar to the claimed compound. Because the superiority of the claimed compound in suppressing action against diarrhea is completely unexpected from Sato, and completely unexpected from Sato's compound 6v, the alleged *prima facie* case of obviousness is rebutted.

Test Example 4 also includes a comparison between Example 1(b) of the present specification and hydrochloride of 5-chloro-7-methyl-2-(4-methyl-1-homopiperazinyl)benzoxazole (E).

Thus, Test Example 4 is also an objective comparison between the claimed subject matter and the closest prior art. *See*, Burckel. In particular, Test Example 4 at pages 39-40 is an objective comparison between the claimed subject matter and Sato's compound 6v in the context of metabolic activity in human liver using an *in vitro* system. Such a comparison is to be given maximum weight in determining the issue of nonobviousness.

The comparison in Test Example 4 demonstrates that the metabolic activity for the claimed compound in human liver using an *in vitro* system is superior to that for Sato's compound 6v. That is, the presently claimed compound is metabolically very stable and is superior in metabolic stability to Sato's compound 6v, which significantly suffered from metabolic degradation. The result of high metabolic stability of the claimed compound would have been unexpected by one of ordinary skill in the art because Sato fails to teach or suggest metabolic stability of compounds disclosed. Furthermore, the result of high metabolic stability is very surprising to one of ordinary skill in the art because an artisan would not have expected that the presence or absence of a methyl group on the nitrogen atom in the homopiperazine ring would result in significant change in metabolic stability of the compounds. Because the superiority of the claimed compound in metabolic stability is completely unexpected from Sato, and completely unexpected from Sato's compound 6v, the alleged *prima facie* case of obviousness is rebutted.

At page 3 of the Action, the Examiner further states:

> Thus, one having ordinary skill in the art would have been motivated to prepare the instantly claimed invention because such structurally homologous compounds are expected to possess similar properties.

At page 3, the Examiner still further states:

> One of ordinary skill in the art would expect that the 5-chloro-2-(1-homopiperazinyl)-7-methylbenzoxazole compound of the instant invention in view of the teachings of SATO to behave in the same

> fashion as the methylated compound, 6v, which is claimed to have the same utility, i.e. irritable bowel syndrome and diarrhea, without the side effects of constipation.

In response, Applicants would like to point out that the statements directly above, such as the remarks that the "compounds are expected to possess ***similar*** properties" and the compounds are expected "to behave in the ***same*** fashion," actually support Applicants' position. That is, these remarks further emphasize that the presently claimed compound's superior suppressing action against diarrhea and the presently claimed compound's superior metabolic stability are completely unexpected from Sato and Sato's compound 6v.

According to the Examiner, one of ordinary skill in the art would have expected the claimed 5-chloro-2-(1-homopiperazinyl)-7-methylbenzoxazole to have the same suppressing action against diarrhea and the same metabolic stability as Sato's compound 6v. Instead, as shown in Test Examples 2 and 4, the presently claimed compound exhibits unexpectedly superior suppressing action and unexpectedly superior metabolic stability.

In conclusion, consistent with the court's decision in Chupp, the presently claimed compound's unexpectedly superior suppressing action against diarrhea and the compound's unexpectedly superior metabolic stability rebuts any *prima facie* case of obviousness. Accordingly, Applicants respectfully request the withdrawal of the §103 rejection of Claims 1 and 18-24 over Sato.

II. Section No. 4: Rejection Under 35 U.S.C. § 103

Claims 1 and 18-24 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over EP 0 806 419 ("EP '419").

As an initial matter, Applicants would like to point out that EP '419 is an equivalent of U.S. Patent No. 6,037,342.

Applicants respectfully traverse this rejection for very similar reasons to those discussed above with respect to Sato.

That is, Applicants would like to point out that the hydrochloride of 5-chloro-7-methyl-2-(4-methyl-1-homopiperazinyl)benzoxazole (E) used in Test Examples 2 and 4 of the specification is the same compound disclosed at page 5, line 19, of EP '419.

Accordingly, the present specification contains objective evidence that the presently claimed compound has unexpectedly superior suppressing action against diarrhea than the compound disclosed at page 5, line 19, of EP '419. Furthermore, the presently claimed compound is metabolically very stable and is superior in metabolic stability to the compound disclosed at page 5, line 19, of EP '419, as shown in the specification. In the specification, the results of comparative examples are disclosed in Examples 2 and 4, in which compound (C) and compound (E) (which are disclosed in the EP publication as compounds of Examples 13 and 37, respectively) were used to demonstrate the unexpectedly high suppressing action against diarrhea of the claimed compound. Furthermore, the claimed compound is shown to have higher metabolic stability than compound (E) in the experiments in the specification.

Thus, consistent with the court's decision in Chupp, the presently claimed compound's unexpectedly superior suppressing action against diarrhea and the compound's unexpectedly superior metabolic stability rebuts any *prima facie* case of obviousness.

At page 4 of the Action, the Examiner states:

> EP '419 is silent to with respect to the metabolic stability of the compounds.

This comment actually supports Applicants' position. That is, the remark emphasizes that the presently claimed compound's superior metabolic stability is completely unexpected from EP '419 and the compound disclosed at page 5, line 19, of EP '419.

At page 4 of the Action, the Examiner also states:

> Furthermore, the metabolic stability of the compounds is not a claim limitation.

The fact that "metabolic stability" is not expressly recited in the present claims is of no

consequence and does not stop the claimed invention from being nonobvious over EP '419.

In determining whether the invention as a whole would have been obvious under 35 U.S.C. § 103, the invention as a whole must be delineated. In re Antonie, 195 USPQ 6, 8 (CCPA 1977)). In delineating the invention as a whole, it is necessary to look not only to the subject matter which is literally recited in the claim in question, but also to those properties of the subject matter which are inherent in the subject matter and are disclosed in the specification. It is the invention as a whole, and not some part of it, which must be obvious under 35 U.S.C. § 103. MPEP §2141.02, at page 2100-122, of Rev. 1, Feb. 2003.

In the present case, the metabolic stability is both inherent to the claimed compound and disclosed in the specification. For example, Test Example 4 shows that the presently claimed compound is metabolically very stable and is superior in metabolic stability to the compound disclosed at page 5, line 19, of EP '419. Accordingly, in delineating the claimed compound as a whole, it is necessary to include not only the subject matter literally recited in Claim 1, but also the properties of the claimed compound, such as its metabolic stability. Because EP '419 is silent with respect to the metabolic stability of the claimed compound, the metabolic stability of the claimed compound is completely unexpected from EP '419, and EP '419 does not render obvious the claimed compound.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this §103 rejection of Claims 1 and 18-24.

III. Section No. 5: Rejection Under 35 U.S.C. § 112

Claims 23 and 24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants have amended Claim 23 and canceled Claim 24, thereby rendering the present §112, first paragraph, rejection moot. Its withdrawal is respectfully requested.

IV. Section No. 6: Rejection Under 35 U.S.C. § 112

Claims 1 and 18-24 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

With respect to the rejection at Section No. 6(a), Claim 1 is drawn to a single compound, i.e., 5-chloro-2-(1-homopiperazinyl)-7-methylbenzoxazole, or a salt thereof. As such, it is respectfully submitted to be in proper format.

With respect to the rejections at Section No. 6(b) and 6(c), Applicants have amended Claims 18 and 19 so that they are drawn to a pharmaceutical composition and a method for the manufacture of the pharmaceutical composition, respectively. Proposed amended Claims 18 and 19 do not recite "medicament," thus rendering the present rejection of Claims 18 and 19 moot.

With respect to the rejections at Section Nos. 6(d), (e) and (f), Claims 21 and 22 are not substantial duplicates of Claim 1.

In this regard, Claim 1 is directed to a single compound, i.e., 5-chloro-2-(1-homopiperazinyl)-7-methylbenzoxazole, or a salt thereof.

Claim 21, on the other hand, is directed to a serotonin 5-HT_3 receptor antagonistic agent. The agent comprises, as an active ingredient, an effective amount of a substance selected from the group consisting of the compound 5-chloro-2-(1-homopiperazinyl)-7-methylbenzoxazole, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof. Accordingly, the scope of Claim 21 is different from that of Claim 1, and the two claims are not substantial duplicates of each other.

Claim 22 is directed to a serotonin 5-HT_3 receptor partial activator. The activator comprises, as an active ingredient, an effective amount of a substance selected from the group consisting of the compound 5-chloro-2-(1-homopiperazinyl)-7-methylbenzoxazole, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof. Accordingly, the scope of Claim 22 is different from that of Claim 1, and the two claims are not substantial duplicates of each other.

With respect to the rejections at Section Nos. 6(g) and (h), Applicants have amended Claim 23 and canceled Claim 24. Amended Claim 23 is directed to an antiemetic agent. The antiemetic agent comprises a substance selected from the group consisting of the compound 5-chloro-2-(1-homopiperazinyl)-7-methylbenzoxazole, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof. Accordingly, the scope of proposed amended Claim 23 is different from that of Claim 1, and the two claims are not substantial duplicates of each other.

V. Section Nos. 7 and 8: Double Patenting Rejections

Claims 1 and 18-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-4 of U.S. Patent No. 6,037,342. Furthermore, Claims 1 and 18-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 3 of co-pending U.S. Application No. 10/219,496.

Applicants respectfully traverse.

As an initial matter, Applicants would like to point out that US '342 is an equivalent of EP '419. Furthermore, the '496 Application is a divisional application in a line of divisional applications having as the parent application the application that issued as US '342. In particular, the '496 Application is the fourth divisional application from US '342.

Accordingly, Claims 1 and 18-24 are not an obviousness-type double patenting of Claims 1-4 of US '342 for the same reasons that EP '419 fails to render obvious Claims 1 and 18-24. That is, the presently claimed compound's unexpectedly superior suppressing action against diarrhea and the compound's unexpectedly superior metabolic stability rebuts any *prima facie* case of obviousness.

Likewise, Claims 1 and 18-24 are not an obviousness-type double patenting of Claim 3 of the '496 Application for the same reasons that EP '419 fails to render obvious Claims 1 and 18-24. Again, the presently claimed compound's unexpectedly superior suppressing action against

diarrhea and the compound's unexpectedly superior metabolic stability rebuts any *prima facie* case of obviousness.

Accordingly, Applicants respectfully request the withdrawal of these obviousness-type double patenting rejections.

VI. Section No. 9: Claim Objection

Claim 19 is objected to under 37 C.F.R. § 1.75(c) as allegedly being in improper form.

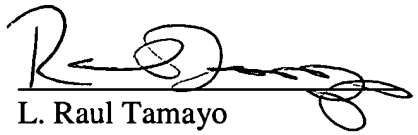
Applicants have amended Claim 19. Proposed amended Claim 19 renders the present object moot. Applicants respectfully request the withdrawal of the objection.

VII. Conclusion

Reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, she is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



L. Raul Tamayo
Registration No. 47,125

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

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